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Article

# Pallado-Catalyzed Cascade Synthesis of 2-Alkoxyquinolines from 1,3-Butadiynamides

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**Abstract:** A novel synthesis strategy to access 2-alkoxyquinoline derivatives via a palladium-driven cascade reaction is disclosed. Unlike classic methods based on the alkylation of 2-quinolones with alkyl halides, the present method benefits from the de novo assembly of the quinoline core starting from 1,3-butadiynamides. Palladium-catalyzed reaction cascades with *N*-(2-iodophenyl)-*N*-tosyl-1,3-butadiynamides and primary alcohols as external nucleophiles proceed under mild reaction conditions and selectively deliver a variety of differently functionalized 4-alkenyl 2-alkoxyquinolines in a single batch transformation.

**Keywords:** 1,3-diyamides; ynamides; [4]cumulenimines; homogeneous catalysis; heterocycles; annulation reactions; cascade reactions; quinolines

## 1. Introduction

The quinoline motif is found in the molecular structure of a large number of drugs, pharmaceuticals and natural products with relevant biological activities [1–4]. Therefore, quinolines serve as a privileged molecular platform for the development of new therapeutic agents. Within these, several differently functionalized 2-alkoxyquinolines have been reported (Figure 1):



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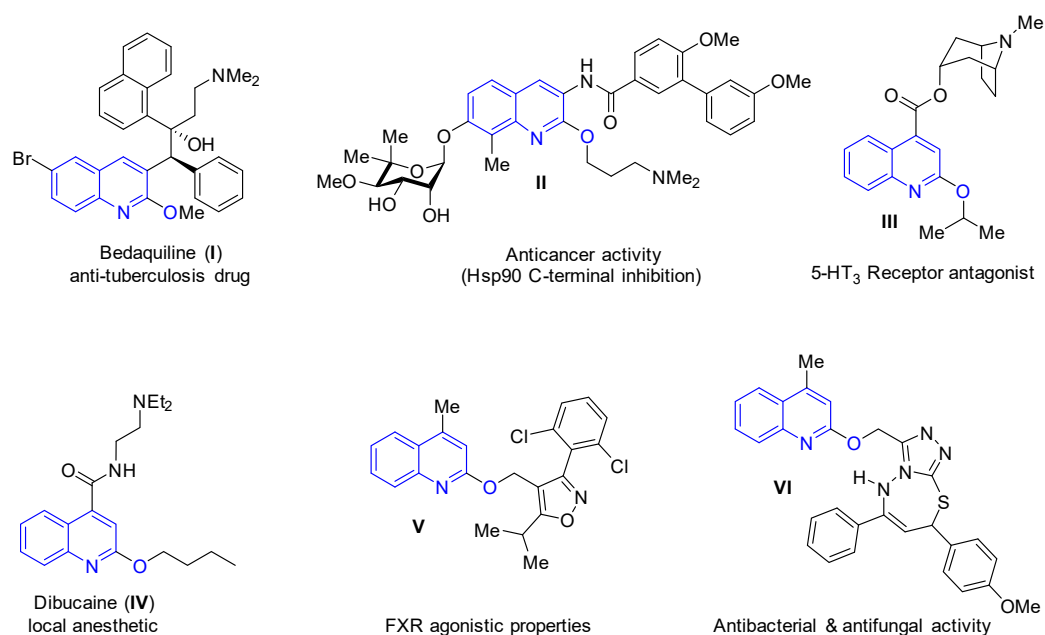
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**Figure 1.** Examples of biologically relevant 2-alkoxyquinoline derivatives.

For instance, bedaquiline **I** has been approved by the U.S. Food and Drug Administration for the treatment of drug-resistant tuberculosis [5]. 2-alkoxyquinoline **II** belongs to a set of novobiocin analogs where the 2-alkoxyquinoline replaces the original coumarin core. **II** displays anticancer activity by targeting the Hsp90 (heat-shock protein 90) C-terminal region (Figure 1) [6]. A series of 2-alkoxyquinolines bearing a lipophilic group at the 1- or 2-position was tested as new 5-HT<sub>3</sub> receptor antagonists, and 2-alkoxyquinoline **III** revealed one of the highest affinities ( $K_i = 0.31$  nM) [7]. 2-*n*-butyloxyquinoline dibucaine **IV** is a local anesthetic [8]. Furthermore, 2-alkoxyquinoline **V** functions as a nonsteroidal agonist of the farnesoid X receptor (FXR) [9], and 2-alkoxyquinoline **VI** is an antibacterial agent [10].

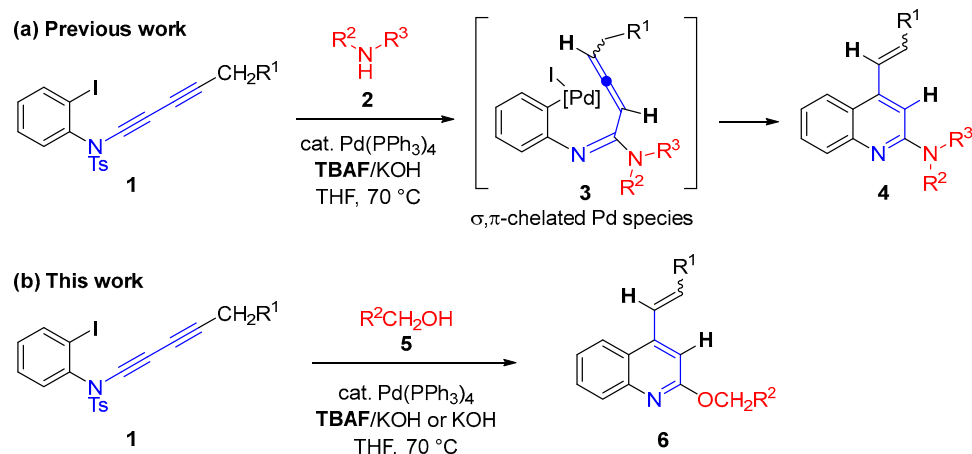
2-Alkoxyquinolines also play a crucial role as ligands in palladium-catalyzed C(sp<sup>3</sup>)-H bond functionalization, notably by enabling primary and secondary C(sp<sup>3</sup>)-H arylation [11,12], as well as  $\gamma$ -C(sp<sup>3</sup>)-H acetoxylation of triflyl-protected amines [13].

Typically, the synthesis of 2-alkoxyquinolines relies on the modification of suitable quinoline derivatives such as 2-chloroquinolines or 2-quinolones. S<sub>N</sub>Ar reactions of 2-chloroquinolines with sodium alkoxides in alcohol deliver 2-alkoxyquinolines after several hours of heating under reflux [14]. Shorter reaction times of a few minutes were reported under microwave irradiation and in polar solvents such as HMPPTA (hexamethylphosphortriamide) or NMP (*N*-methylpyrrolidone) [15]. Another classic synthesis method involves base-mediated *O*-alkylations of 2-quinolones by alkyl halides [6]. However, 2-quinolones are ambident nucleophiles due to their two tautomeric forms: 2-quinolone and 2-hydroxyquinoline. Here, the control of selectivity of *O*- versus *N*-alkylation is a non-negligible issue. Typically, *O*-alkylated products are obtained through the use of a stoichiometric amount of silver salts (Ag<sub>2</sub>CO<sub>3</sub>) [16,17]. The preferential interaction of the silver cation with the N atom ensures blocking of the *N*-site and liberates the *O*-nucleophilic site for *O*-alkylations. Recently, chemoselective Pd-catalyzed *O*-benzylations of 2-quinolones were achieved without the need of stoichiometric amounts of silver salts [18]. This process relies on the use of XantPhosPdCl<sub>2</sub> as the pre-catalyst and the generation of a phosphine mono-oxide Pd(II)  $\eta^1$ -benzyl complex as the key intermediate. However, the method is not applicable to alkyl halides other than benzyl halides. Whereas a variety of annulation reactions involving nonconventional bond-forming reactions have been developed for functionalized 2-quinolones [19,20], direct routes to 2-alkoxyquinolines based on the assembly of the quinoline core are rare. As an example, Brandsma described the synthesis of 2-*O*-silylated quinolines resulting from the reaction of phenyl isocyanate with lithiated allenes [21]. More recently, the DMAP-catalyzed synthesis of tert-butylquinolin-2-yl carbonates from 2-alkenylanilines and di-tert-butyl dicarbonate was reported [22].

Within our research on the chemistry of ynamides [23–28] and 1,3-butadiynamides [29–31], we recently disclosed a straightforward route to functionalized 2-amino-4-alkenylquinolines **4** from 1,3-butadiynamides **1** based on a palladium-catalyzed reaction cascade with primary or secondary amines **2** as external nucleophiles (Scheme 1a) [32].

The presence of TBAF (tetrabutylammonium fluoride) and KOH induces the cleavage of the tosyl group located at the ynamide nitrogen atom and ensures the involvement of both triple bonds in the annulation reaction cascade via the postulated  $\sigma,\pi$ -chelated Pd-species **3** as the key intermediate.

Extending the scope of this Pd-catalyzed cascade reaction is an attractive aim. When using readily available alcohols as nucleophiles, it would likely lead to a new approach to versatile 2-alkoxyquinolines via straightforward annulation reactions. We report here that primary alcohols **5** can indeed serve as suitable nucleophiles and reaction partners to convert readily accessible 1,3-butadiynamides **1** into functionalized 4-alkenyl 2-alkoxyquinolines **6** within a single batch and under mild conditions (Scheme 1b).



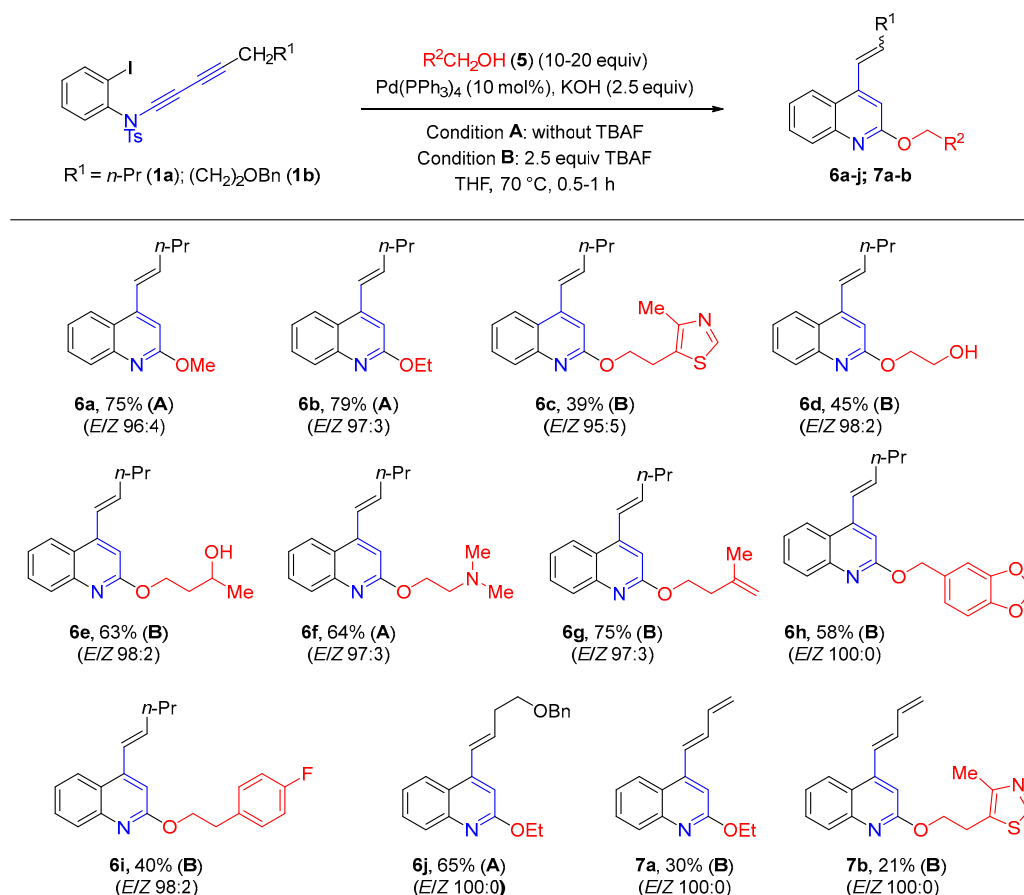
**Scheme 1.** (a) Pd-catalyzed cascade reaction of 1,3-butadiynamides **1** with primary or secondary amines **2** leading to 2-amino-4-alkenyl quinolines **4**. (b) Pd-catalyzed cascade reaction of 1,3-butadiynamides **1** with primary alcohols **5** yielding 2-alkoxy-4-alkenyl quinolines **6**.

## 2. Results and Discussion

In our work related to the synthesis of 2-aminoquinolines **4**, where primary or secondary amines served as nucleophiles, TBAF was added to the reaction to improve the solubility of KOH in THF through anion metathesis. Considering that the solubility of KOH is enhanced in methanol, the reaction of 1,3-butadiynamide **1a** ( $R^1 = n\text{-Pr}$ ) was attempted without TBAF. Fortunately, diynamide **1a** was now fully converted into the expected 4-alkenyl 2-methoxyquinoline **6a** in the presence of  $\text{Pd}(\text{PPh}_3)_4$  (10 mol%) and KOH (2.5 equiv) in methanol at 70 °C (Scheme 2). The 2-methoxyquinoline **6a** was obtained in 75% yield with an (*E*)/(*Z*) ratio of 96:4 after column chromatography. Similarly, the 2-ethoxy analogue **6b** was obtained in 79% isolated yield with an (*E*)/(*Z*) ratio of 97:3 when the reaction was carried out in EtOH as the solvent (Scheme 2). Notably, the yield of isolated **6b** was not affected when the amount of EtOH was reduced from 165 to 10 equivalents and using THF as the solvent.

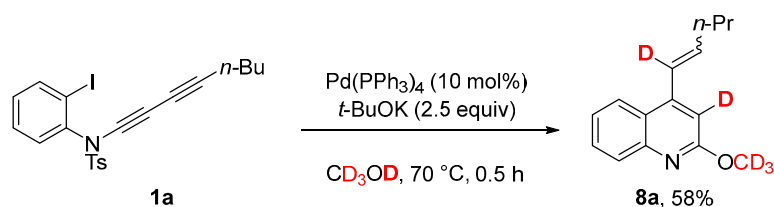
The option for utilizing more sophisticated alcohols was evaluated with 4-methylthiazol-5-yl-ethanol (**5c**). No reaction occurred between **1a** and alcohol **5c** (10 equiv) in THF after 1 h of heating at 70 °C and recovering the starting material **1a**. This result might be due to the lack of solubility of KOH in the reaction medium. The addition of EtOH or MeOH to solubilize KOH could not be considered as these might compete as nucleophiles in this reaction. Therefore, the use of TBAF/KOH to induce an anion metathesis was again attempted. The reaction of **1a** (0.11 mmol) with alcohol **5c** (20 equiv) was performed in 1 mL of a commercially available 1M solution of TBAF in THF (9.5 equiv) in the presence of 10 mol% of  $\text{Pd}(\text{PPh}_3)_4$  and 2.5 equivalents of KOH. Gratifyingly, under these modified reaction conditions, the expected 2-alkoxyquinoline **6c** was obtained in 39% yield of the isolated material after 1 h at 70 °C (Scheme 2). The scope of this new 2-alkoxyquinoline synthesis was further studied using 10 mol% of  $\text{Pd}(\text{PPh}_3)_4$ , 2.5 equiv of KOH and 2.5 equiv of TBAF in THF as the standard reaction conditions. When glycol (**5d**) was used as the *O*-nucleophile, the product of mono-addition **6d** was the sole product obtained (45% yield). The reaction was chemoselective with 1,3-butanediol (**5e**). Here, the primary alcohol reacted exclusively to give the corresponding 2-alkoxyquinoline **6e** in 63% yield. It is worthy of note that access to quinolines **6d** and **6e** is not as straightforward using classic methods. Reactions with secondary or tertiary alcohols (i.e., cyclopentanol and tert-butanol, respectively) failed, probably due to steric reasons. On the other hand, alcohols tethered to an amino group, an olefin or an electron-rich or electron-poor aryl group were successfully engaged in this new and unprecedented 2-alkoxyquinoline synthesis and yielded a set of 2-alkoxy-4-alkenyl quinolines **6f-i** in 40 to 75% yields of the isolated compounds (Scheme 2). In all cases, the (*E*) isomer was preferentially formed with an (*E*)/(*Z*) ratio higher than 95:5. The reaction of diynamide **1b** ( $R^1 = (\text{CH}_2)_2\text{OBn}$ ) in EtOH as the solvent selectively

led to the (*E*) isomer of the corresponding quinoline **6j** in 65% yield of the isolated product. Interestingly, when the reaction was conducted in the presence of TBAF (2.5 equiv, condition B), the product was not **6j** but 2-ethoxy-4-dienylquinoline **7a**—the product resulting from the elimination of benzyl alcohol. Quinoline **7a** was obtained in 30% yield via this extended reaction cascade, which terminates with the elimination of benzyl alcohol. Similarly, the reaction of **1b** with 4-methyl-thiazol-5-yl-ethanol (**5c**) in the presence of TBAF yielded 4-dienyl-2-ethoxyquinoline **7b** as the major product in 21% yield.



**Scheme 2.** Synthesis of 2-alkoxy-4-alkenylquinolines **6** and 2-alkoxy-4-dienylquinolines **7a,b**.

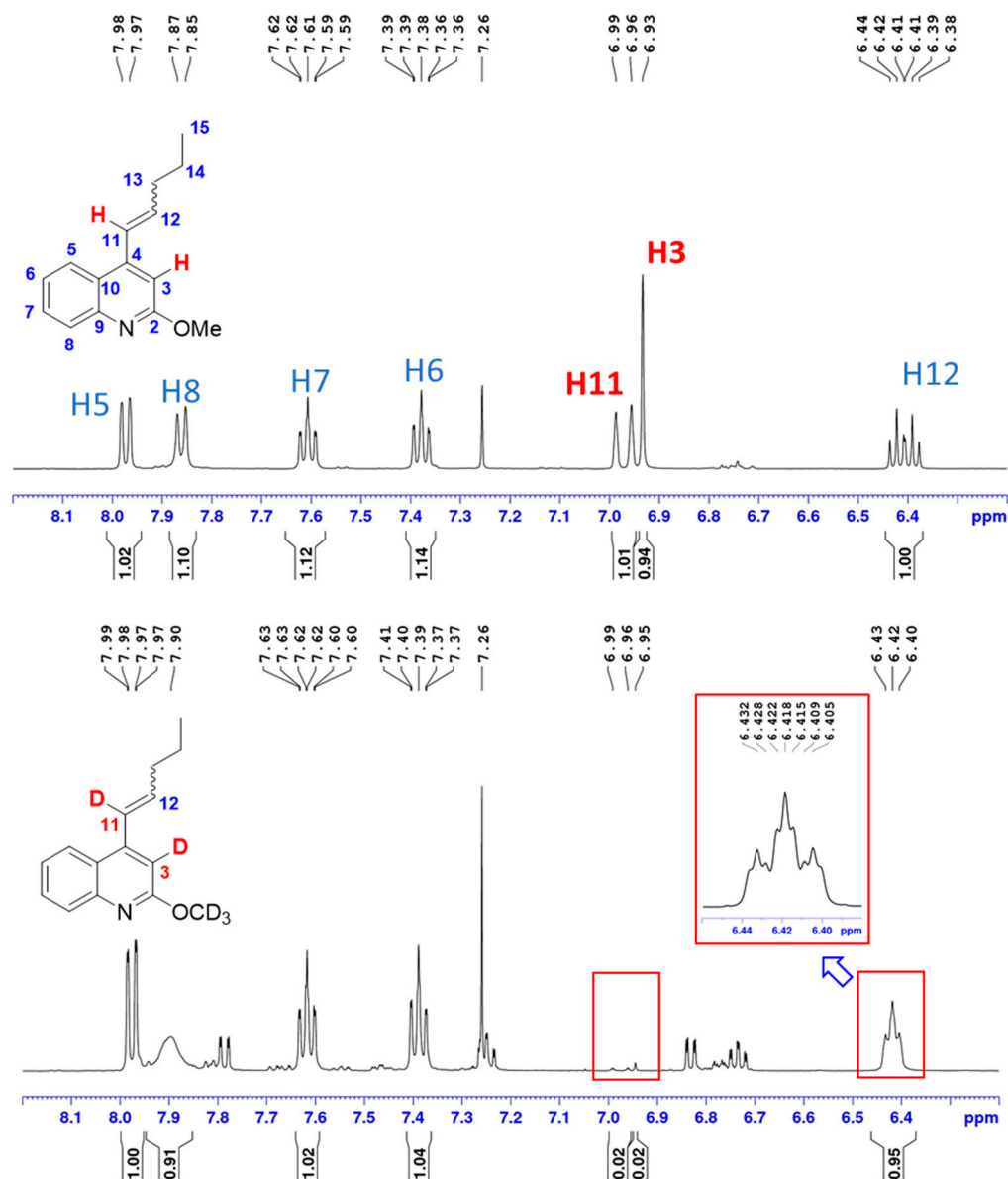
A deuterium labeling experiment was carried out with diynamide **1a** in CD<sub>3</sub>OD using *t*-BuOK as the base instead of KOH to avoid any proton source (Scheme 3).



**Scheme 3.** Deuterium labeling experiment.

The resulting penta-deuterated quinoline **8a** was isolated in 58% yield. The comparison of the <sup>1</sup>H NMR spectrum of **8a** with that of non-deuterated quinoline **6a** provided evidence of the selective incorporation of deuterium into the C3 and C11 positions (Scheme 4). The <sup>1</sup>H NMR signals at  $\delta = 6.93$  (s, H-3) and 6.97 (d, H-11) for the non-deuterated quinoline **6a** almost disappeared in the <sup>1</sup>H NMR spectrum of **8a**. Moreover, the multiplicity of the signal assigned to the olefinic proton H-12 at  $\delta = 6.41$  was altered from a doublet of triplets

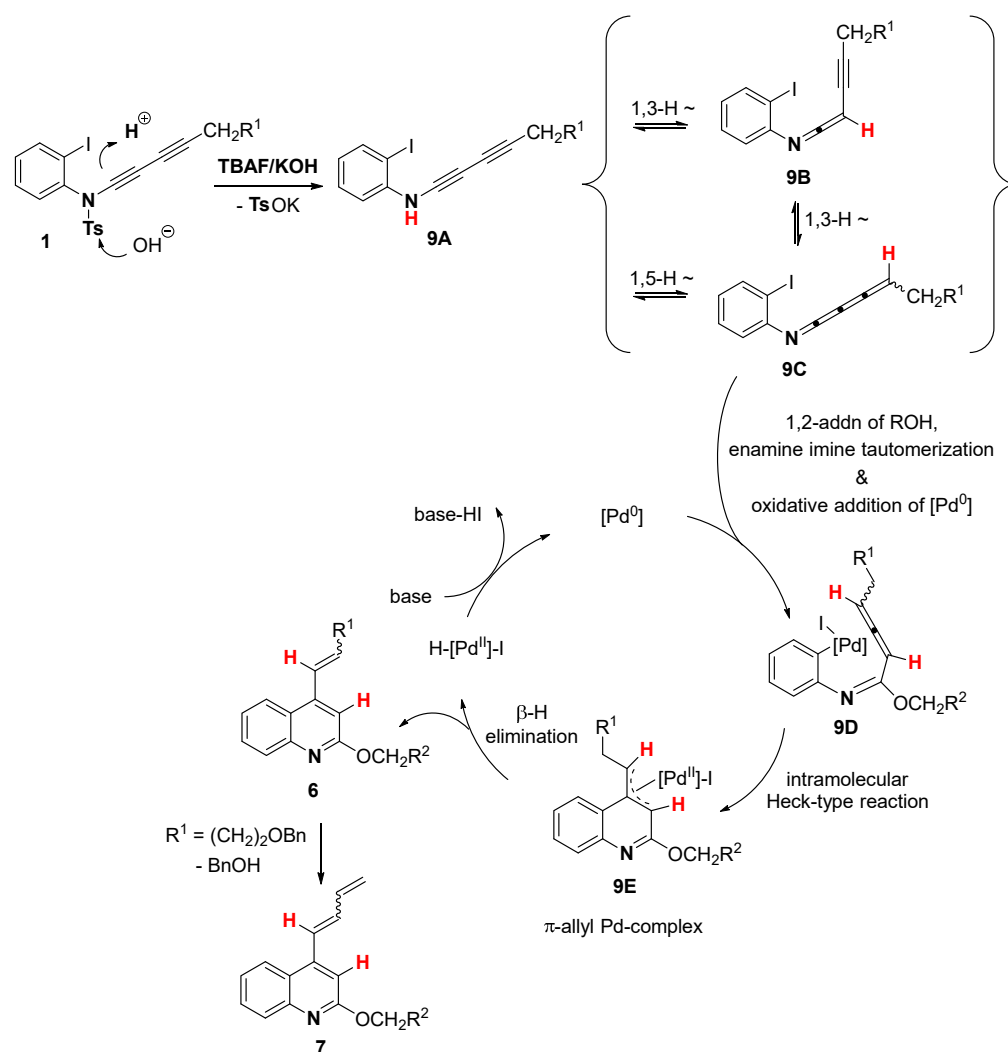
with  $^3J_{H,H} = 15.5$  Hz and  $^3J_{H,H} = 7.0$  Hz to a triplet of triplets with  $^3J_{H,H} = 7.0$  Hz and  $^3J_{H,D(trans)} = 2.0$  Hz. The clear loss of the  $^1H$  signals at  $\delta = 6.93$  and  $6.97$ , as well as the clear changes in the spin-system of the proton signal at  $\delta = 6.41$  in the  $^1H$  NMR spectra indicate an almost complete incorporation of deuterium at those positions.



**Scheme 4.** Comparison of the  $^1H$  NMR ( $CDCl_3$ , 500 MHz) spectra of quinolines **6a** (top) and **8a** (bottom). Only the  $\delta = 6.2$ – $8.2$  ppm range is shown for reasons of clarity.

The deuterium labelling experiment supports well the proposed mechanism outlined in Scheme 5. Presumably, the combination of alcohol **5**/KOH or **5**/TBAF/KOH cleaves the tosyl group located at the ynamide nitrogen atom (**1**  $\rightarrow$  **9A**) and initiates the subsequent cascade reaction (Scheme 5). The resulting 1,3-butadiynamine **9A** is in equilibrium with the alkynyl ketenimine **9B** and the [4]-cumulenimine **9C** with formal 1,3- and 1,5-H shifts, respectively. Selective 1,2-addition of alcohol **5** to either imine **9B** or **9C** followed by enamine-imine tautomerization—and isomerization of the propargyl to an allene moiety in the case of **9B**—delivers the allene-derived intermediate **9D** after oxidative addition of the palladium(0) catalyst. Whether the oxidative addition of palladium(0) already occurs with intermediates **9A**–**C** and therefore facilitates the isomerization sequence or whether oxidative addition takes place after the 1,3-diyndamine-to-allenyl-imine isomerization remains an

open question. However, once the  $\sigma,\pi$ -chelated palladium intermediate **9D** is formed, a subsequent intramolecular Heck-type reaction furnishes the annulated  $\pi$ -allyl palladium species **9E**, which undergoes  $\beta$ -hydrogen elimination to produce 4-alkenyl quinolines **6** along with the palladium–hydride complex. Reduction of the latter by the base allows the regeneration of the Pd(0) active catalyst. Interestingly, in the case of 1,3-butadiynamide **1b** ( $R^1 = (\text{CH}_2)_2\text{OBn}$ ), the reaction conditions indicated by B favor in situ elimination of benzyl alcohol and yield 2-alkoxy-4-(1,3-dienyl)quinolines **7** as the major products. Here, the formation of the conjugated 1,3-butadiene moiety is most likely the underlying driving force.



**Scheme 5.** Proposed mechanism for the synthesis of 2-alkoxy-4-alkenylquinolines **6** and 2-alkoxy-4-(1,3-dienyl)quinolines **7**.

### 3. Materials and Methods

Chromatographic purification steps were performed using Acros Organics silica gel Si 60 (40–60  $\mu\text{m}$ ) or Merck aluminum oxide 90 active neutral (60–200  $\mu\text{m}$ , activity stage III). Thin-layer chromatography (TLC) was developed on Merck silica gel 60 plates (0.20 mm) or on aluminum oxide 60 neutral plates (0.20 mm) with UV detection (Merck, Kenilworth, NJ, USA). Nuclear magnetic resonance (NMR) spectra were recorded on a BRUKER AVANCE III 500 (500 MHz) or a BRUKER NEO 600 (600 MHz) spectrometer (Bruker, Billerica, Kenilworth, MA, USA).  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts ( $\delta$ ) are given in ppm (parts per million) using the TMS signal (0 ppm) and the residual peak of chloroform-D (77.16 ppm), respectively, as the internal reference (see Supplementary Materials). Coupling constants

are reported in Hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, sext = sextuplet, m = multiplet, br = broad). The (*E*)/(*Z*) isomer ratio was determined for each quinoline from the <sup>1</sup>H NMR spectrum via integration of the dt signals of the olefin proton of both isomers. High-resolution mass spectrometry (HRMS) analysis was performed in electron spray ionization (ESI) mode on an Acquity UPLC H-ClassXevo G2-XS QToF (WATERS) spectrometer (Waters, Milford, MA, USA). Melting points (Mp) were measured with an electrothermal apparatus and are not corrected. The procedure for the synthesis of 1,3-butadiynamides **1a,b** and their characterization data were reported [32,33].

### 3.1. General Procedure for the Synthesis of 2-Alkoxyquinolines **6a–b, f, j** (Condition A)

1,3-butadiynamide **1** (0.11 mmol), KOH (15 mg, 0.26 mmol, 2.5 equiv), tetrakis (triphenylphosphine)palladium(0) (Pd(PPh<sub>3</sub>)<sub>4</sub>) (12 mg, 10 mol%) and alcohol **5** (1 mL) were introduced in a dry Schlenk tube under an argon atmosphere. The Schlenk tube was immediately placed in an oil bath preheated to 70 °C. After 1 h, CH<sub>2</sub>Cl<sub>2</sub> and brine were added to the reaction mixture. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic layers were dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure. The product was purified via silica gel or alumina column chromatography.

**2-Methoxy-4-(pent-1-en-1-yl)quinoline (6a)**. Prepared from *N*-(2-iodophenyl)-4-methyl-*N*-(octa-1,3-diyn-1-yl)benzenesulfonamide (**1a**) (50 mg, 0.105 mmol) and MeOH (**5a**) (1 mL). The product was purified via column chromatography (Al<sub>2</sub>O<sub>3</sub>, *n*-pentane/Et<sub>2</sub>O 20:1 (*v/v*)) to yield **6a** as an oil (18 mg, 0.08 mmol, yield: 75%, *E/Z* = 96:4). *R*<sub>f</sub> = 0.53 (*n*-pentane/Et<sub>2</sub>O = 20:1 (*v/v*)). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.97 (d, <sup>3</sup>*J* = 7.9 Hz, 1 H), 7.86 (d, <sup>3</sup>*J* = 8.3 Hz, 1 H), 7.61 (ddd, <sup>3</sup>*J* = 8.3 Hz, <sup>3</sup>*J* = 7.0 Hz, <sup>4</sup>*J* = 1.2 Hz, 1 H), 7.38 (ddd, <sup>3</sup>*J* = 8.1 Hz, <sup>3</sup>*J* = 7.0 Hz, <sup>4</sup>*J* = 1.3 Hz, 1 H), 6.97 (d, <sup>3</sup>*J* = 15.7 Hz, 1 H), 6.93 (s, 1 H), 6.41 (dt, <sup>3</sup>*J* = 15.5 Hz, <sup>3</sup>*J* = 7.0 Hz, 1 H), 4.07 (s, 3 H), 2.31 (m, 2 H), 1.57 (sext, <sup>3</sup>*J* = 7.4 Hz, 2 H) and 1.00 (t, <sup>3</sup>*J* = 7.4 Hz, 3 H). Identified <sup>1</sup>H NMR signals corresponding to the minor isomer: 6.02 (dt, <sup>3</sup>*J* = 11.6 Hz, <sup>3</sup>*J* = 7.5 Hz, 1 H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 162.7 (C), 147.1 (C), 146.7 (C), 138.0 (CH), 129.4 (CH), 127.8 (CH), 124.9 (CH), 123.89 (CH), 123.85 (C), 123.8 (CH), 108.7 (CH), 53.4 (CH<sub>3</sub>), 35.6 (CH<sub>2</sub>), 22.4 (CH<sub>2</sub>) and 13.9 (CH<sub>3</sub>). HRMS (ESI+): Calc'd for C<sub>15</sub>H<sub>18</sub>NO [M + H]<sup>+</sup>: 228.1388; found: 228.1395.

**2-Ethoxy-4-(pent-1-en-1-yl)quinoline (6b)**. Prepared from **1a** (50 mg, 0.105 mmol) in EtOH (**5b**) (1 mL). The product was purified via column chromatography (Al<sub>2</sub>O<sub>3</sub>, *n*-pentane/Et<sub>2</sub>O 20:1 (*v/v*)) to yield **6b** as an oil (20 mg, 0.083 mmol, yield: 79%, *E/Z* = 97:3). *R*<sub>f</sub> = 0.62 (*n*-pentane/Et<sub>2</sub>O = 20:1 (*v/v*)). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.96 (dd, <sup>3</sup>*J* = 8.3 Hz, <sup>4</sup>*J* = 1.1 Hz, 1 H), 7.83 (d, <sup>3</sup>*J* = 8.3 Hz, 1 H), 7.59 (ddd, <sup>3</sup>*J* = 8.3 Hz, <sup>3</sup>*J* = 6.9 Hz, <sup>4</sup>*J* = 1.4 Hz, 1 H), 7.36 (ddd, <sup>3</sup>*J* = 8.2 Hz, <sup>3</sup>*J* = 7.0 Hz, <sup>4</sup>*J* = 1.3 Hz, 1 H), 6.97 (d, <sup>3</sup>*J* = 15.6 Hz, 1 H), 6.93 (s, 1 H), 6.41 (dt, <sup>3</sup>*J* = 15.5 Hz, <sup>3</sup>*J* = 7.0 Hz, 1 H), 4.53 (q, <sup>3</sup>*J* = 7.1 Hz, 2 H), 2.30 (m, 2 H), 1.57 (sext, <sup>3</sup>*J* = 7.4 Hz, 2 H), 1.45 (t, <sup>3</sup>*J* = 7.1 Hz, 3 H) and 1.00 (t, <sup>3</sup>*J* = 7.4 Hz, 3 H). Identified <sup>1</sup>H NMR signals corresponding to the minor isomer: 6.01 (dt, <sup>3</sup>*J* = 11.6 Hz, <sup>3</sup>*J* = 7.5 Hz, 1 H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 162.4 (C), 147.2 (C), 146.6 (C), 137.8 (CH), 129.4 (CH), 127.8 (CH), 124.9 (CH), 123.78 (C), 123.76 (CH), 123.7 (CH), 108.9 (CH), 61.7 (CH<sub>2</sub>), 35.6 (CH<sub>2</sub>), 22.4 (CH<sub>2</sub>), 14.8 (CH<sub>3</sub>) and 13.9 (CH<sub>3</sub>). HRMS (ESI+): Calc'd for C<sub>16</sub>H<sub>20</sub>NO [M + H]<sup>+</sup>: 242.1545; found: 242.1547.

***N,N*-Dimethyl-2-((4-(pent-1-en-1-yl)quinolin-2-yl)oxy)ethanamine (6f)**. Prepared from **1a** (50 mg, 0.105 mmol) and 3-(dimethylamino)propan-1-ol (**5f**) (105 μL, 1.1 mmol, 10 equiv) in dry THF (1 mL). The reaction was complete after 30 min at 70 °C. The product was purified via column chromatography (Al<sub>2</sub>O<sub>3</sub>, *n*-pentane/EtOAc/Et<sub>3</sub>N 90:10:1 (*v/v/v*)) to yield **6f** (19 mg, 0.067 mmol, yield: 64%, *E/Z* = 97:3) as an oil. *R*<sub>f</sub> = 0.37 (*n*-pentane/EtOAc/Et<sub>3</sub>N 90:10:1 (*v/v/v*)). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.97 (dd, <sup>3</sup>*J* = 8.3 Hz, <sup>4</sup>*J* = 1.0 Hz, 1 H), 7.82 (d, <sup>3</sup>*J* = 8.3 Hz, 1 H), 7.59 (ddd, <sup>3</sup>*J* = 8.4 Hz, <sup>3</sup>*J* = 7.0 Hz, <sup>4</sup>*J* = 1.4 Hz, 1 H), 7.37 (ddd, <sup>3</sup>*J* = 8.2 Hz, <sup>3</sup>*J* = 7.0 Hz, <sup>4</sup>*J* = 1.2 Hz, 1 H), 7.01 (s, 1 H), 6.97 (d, <sup>3</sup>*J* = 15.6 Hz, 1 H), 6.40 (dt, <sup>3</sup>*J* = 15.6 Hz, <sup>3</sup>*J* = 7.0 Hz, 1 H), 4.59 (t, <sup>3</sup>*J* = 5.6 Hz, 2 H), 2.78 (t, <sup>3</sup>*J* = 5.6 Hz, 2 H), 2.37 (s, 6 H), 2.30 (m, 2 H), 1.56 (sext, <sup>3</sup>*J* = 7.3 Hz, 2 H) and 1.00 (t, <sup>3</sup>*J* = 7.3 Hz, 3 H). Identified <sup>1</sup>H



NMR signals corresponding to the minor isomer: 6.01 (dt,  $^3J = 11.6$  Hz,  $^3J = 7.4$  Hz, 1 H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  162.3 (C), 147.1 (C), 146.5 (C), 137.9 (CH), 129.3 (CH), 127.8 (CH), 124.8 (CH), 123.9 (C), 123.8 (CH), 123.7 (CH), 109.1 (CH), 63.2 ( $\text{CH}_2$ ), 58.4 ( $\text{CH}_2$ ), 45.9 ( $\text{CH}_3$ ), 35.5 ( $\text{CH}_2$ ), 22.4 ( $\text{CH}_2$ ) and 13.8 ( $\text{CH}_3$ ). HRMS (ESI+): Calc'd for  $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}$  [ $\text{M} + \text{H}$ ] $^+$ : 285.1967; found: 285.1968.

(*E*)-4-(4-(Benzyloxy)but-1-en-1-yl)-2-ethoxyquinoline (**6j**). Prepared from *N*-(7-(benzyloxy)hepta-1,3-dien-1-yl)-*N*-(2-iodophenyl)-4-methylbenzenesulfonamide (**1b**) (50 mg, 0.088 mmol) in EtOH (1 mL). The reaction was complete after 30 min at 70 °C. The product was purified via column chromatography ( $\text{SiO}_2$ , *n*-pentane/ $\text{Et}_2\text{O}$  20:1 (*v/v*)) to yield (*E*)-**6j** as an oil (19 mg, 0.057 mmol, yield: 65%).  $R_f = 0.25$  (*n*-pentane/ $\text{Et}_2\text{O}$  20:1 (*v/v*)).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (d,  $^3J = 8.2$  Hz, 1 H), 7.82 (d,  $^3J = 8.3$  Hz, 1 H), 7.60 (dd,  $^3J = 8.0$  Hz,  $^3J = 7.1$  Hz, 1 H), 7.36–7.28 (m, 6 H), 7.05 (d,  $^3J = 15.7$  Hz, 1 H), 6.93 (s, 1 H), 6.43 (dt,  $^3J = 15.6$  Hz,  $^3J = 7.0$  Hz, 1 H), 4.57 (s, 2 H), 4.52 (q,  $^3J = 7.1$  Hz, 2 H), 3.66 (t,  $^3J = 6.5$  Hz, 2 H), 2.65 (m, 2 H) and 1.45 (t,  $^3J = 7.1$  Hz, 3 H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  162.4 (C), 147.2 (C), 146.2 (C), 138.4 (C), 134.0 (CH), 129.4 (CH), 128.6 (CH), 127.9 (CH), 127.82 (CH), 127.80 (CH), 126.6 (CH), 123.8 (CH), 123.72 (CH), 123.69 (C), 109.1 (CH), 73.2 ( $\text{CH}_2$ ), 69.5 ( $\text{CH}_2$ ), 61.6 ( $\text{CH}_2$ ), 34.0 ( $\text{CH}_2$ ) and 14.8 ( $\text{CH}_3$ ). HRMS (ESI+): Calc'd for  $\text{C}_{22}\text{H}_{24}\text{NO}_2$  [ $\text{M} + \text{H}$ ] $^+$ : 334.1807; found: 334.1808.

### 3.2. General Procedure for the Synthesis of 2-Alkoxyquinolines **6c–e**, **g–i** and **7a–b** (Condition B)

1,3-butadienamide **1** (0.11 mmol), KOH (15 mg, 0.26 mmol, 2.5 equiv),  $\text{Pd}(\text{PPh}_3)_4$  (12 mg, 10 mol%), alcohol **5** (10–20 equiv), tetra-*n*-butylammonium fluoride (TBAF) 1M solution in THF (0.3 mL, 0.3 mmol, 2.5 equiv) and dry THF (1 mL) were introduced in a Schlenk tube under an argon atmosphere. The Schlenk tube was immediately placed in an oil bath preheated to 70 °C. Upon completion of the reaction (0.5 to 1 h),  $\text{CH}_2\text{Cl}_2$  and brine were added to the reaction mixture. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organic layers were dried ( $\text{MgSO}_4$ ), filtered and evaporated under reduced pressure. The product was purified via silica gel or alumina column chromatography.

4-Methyl-5-(2-((4-(pent-1-en-1-yl)quinolin-2-yl)oxy)ethyl)thiazole (**6c**). Prepared from **1a** (50 mg, 0.105 mmol) and 2-(4-methylthiazol-5-yl)ethanol (**5c**) (0.25 mL, 2.1 mmol, 20 equiv) in 1 mL of 1M tetra-*n*-butylammonium fluoride (TBAF) solution in THF (1 mmol, 9.5 equiv). The reaction was complete after 1 h at 70 °C. The product was purified via column chromatography ( $\text{SiO}_2$ , *n*-pentane/ $\text{EtOAc}/\text{Et}_3\text{N}$  90:10:1 (*v/v/v*)) to yield **6c** as an oil (14 mg, 0.041 mmol, yield: 39%, *E/Z* = 95:5).  $R_f = 0.20$  (*n*-pentane/ $\text{EtOAc}/\text{Et}_3\text{N}$  90:10:1 (*v/v/v*)).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.59 (s, 1 H), 7.98 (dd,  $^3J = 8.3$  Hz,  $^4J = 1.0$  Hz, 1 H), 7.82 (d,  $^3J = 8.3$  Hz, 1 H), 7.61 (ddd,  $^3J = 8.3$  Hz,  $^3J = 7.0$  Hz,  $^4J = 1.4$  Hz, 1 H), 7.38 (ddd,  $^3J = 8.2$  Hz,  $^3J = 7.0$  Hz,  $^4J = 1.3$  Hz, 1 H), 6.98 (d,  $^3J = 15.8$  Hz, 1 H), 6.93 (s, 1 H), 6.42 (dt,  $^3J = 15.6$  Hz,  $^3J = 7.0$  Hz, 1 H), 4.64 (t,  $^3J = 6.7$  Hz, 2 H), 3.30 (t,  $^3J = 6.7$  Hz, 2 H), 2.48 (s, 3 H), 2.32 (m, 2 H), 1.58 (sext,  $^3J = 7.3$  Hz, 2 H) and 1.01 (t,  $^3J = 7.4$  Hz, 3 H). Identified  $^1\text{H}$  NMR signals corresponding to the minor isomer: 6.03 (dt,  $^3J = 11.6$  Hz,  $^3J = 7.5$  Hz, 1 H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  161.8 (C), 149.9 (C), 149.8 (CH), 147.0 (C), 146.9 (C), 138.1 (CH), 129.5 (CH), 127.8 (CH), 127.7 (C), 124.8 (CH), 124.0 (CH), 123.9 (C), 123.8 (CH), 108.6 (CH), 65.4 ( $\text{CH}_2$ ), 35.6 ( $\text{CH}_2$ ), 26.3 ( $\text{CH}_2$ ), 22.4 ( $\text{CH}_2$ ), 15.2 ( $\text{CH}_3$ ) and 13.9 ( $\text{CH}_3$ ). HRMS (ESI+): Calc'd for  $\text{C}_{20}\text{H}_{23}\text{N}_2\text{OS}$  [ $\text{M} + \text{H}$ ] $^+$ : 339.1531; found: 339.1530.

2-((4-(pent-1-en-1-yl)quinolin-2-yl)oxy)ethanol (**6d**). Prepared from **1a** (50 mg, 0.105 mmol) and ethylene glycol (**5d**) (120  $\mu\text{L}$ , 2.1 mmol, 20 equiv). The reaction was complete after 1 h at 70 °C. The product was purified via column chromatography ( $\text{SiO}_2$ , *n*-pentane/ $\text{EtOAc}/\text{Et}_3\text{N}$  80:20:1 (*v/v/v*) to 60:40:1 (*v/v/v*)) to yield **6d** as an oil (12 mg, 0.047 mmol, yield: 45%, *E/Z* = 98:2).  $R_f = 0.17$  (pentane/ $\text{EtOAc}/\text{Et}_3\text{N}$  80:20:1 (*v/v/v*)).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98 (d,  $^3J = 8.2$  Hz, 1 H), 7.80 (d,  $^3J = 8.2$  Hz, 1 H), 7.62 (ddd,  $^3J = 8.3$  Hz,  $^3J = 7.0$  Hz,  $^4J = 1.3$  Hz, 1 H), 7.40 (ddd,  $^3J = 8.2$  Hz,  $^3J = 7.0$  Hz,  $^4J = 1.1$  Hz, 1 H), 6.99 (s, 1 H), 6.98 (d,  $^3J = 15.4$  Hz, 1 H), 6.43 (dt,  $^3J = 15.4$  Hz,  $^3J = 7.0$  Hz, 1 H), 4.74 (br s, 1 H), 4.64 (m, 2 H), 4.00 (m, 2 H), 2.32 (m, 2 H), 1.57 (sext,  $^3J = 7.4$  Hz, 2 H) and 1.00 (t,  $^3J = 7.4$  Hz, 3 H). Identified  $^1\text{H}$  NMR signals corresponding to the minor isomer: 6.05 (dt,  $^3J = 11.6$  Hz,  $^3J = 7.4$  Hz, 1 H).

$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  162.6 (C), 147.5 (C), 146.3 (C), 138.5 (CH), 129.8 (CH), 127.3 (CH), 124.7 (CH), 124.3 (CH), 123.9 (C), 123.8 (CH), 108.8 (CH), 69.6 ( $\text{CH}_2$ ), 63.1 ( $\text{CH}_2$ ), 35.6 ( $\text{CH}_2$ ), 22.3 ( $\text{CH}_2$ ) and 13.9 ( $\text{CH}_3$ ). HRMS (ESI+): Calc'd for  $\text{C}_{16}\text{H}_{20}\text{NO}_2$  [ $\text{M} + \text{H}$ ] $^+$ : 258.1494; found: 258.1497.

4-((4-(pent-1-en-1-yl)quinolin-2-yl)oxy)butan-2-ol (**6e**). Prepared from **1a** (50 mg, 0.105 mmol) and 1,3-butanediol (**5e**) (190  $\mu\text{L}$ , 2.1 mmol, 20 equiv). The reaction was complete after 40 min at 70  $^\circ\text{C}$ . The product was purified via column chromatography ( $\text{SiO}_2$ , *n*-pentane/AcOEt/ $\text{Et}_3\text{N}$  90:10:1 (*v/v/v*) to 80:20:1 (*v/v/v*)) to yield **6e** as an oil (19 mg, 0.067 mmol, yield: 63%, *E/Z* = 98:2).  $R_f$  = 0.65 (*n*-pentane/AcOEt 6:4 (*v/v*)).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98 (dd,  $^3J$  = 8.3 Hz,  $^4J$  = 1.1 Hz, 1 H), 7.80 (d,  $^3J$  = 8.2 Hz, 1 H), 7.61 (ddd,  $^3J$  = 8.3 Hz,  $^3J$  = 7.0 Hz,  $^4J$  = 1.4 Hz, 1 H), 7.39 (ddd,  $^3J$  = 8.2 Hz,  $^3J$  = 7.0 Hz,  $^4J$  = 1.3 Hz, 1 H), 6.97 (d,  $^3J$  = 15.6 Hz, 1 H), 6.93 (s, 1 H), 6.43 (dt,  $^3J$  = 15.5 Hz,  $^3J$  = 7.0 Hz, 1 H), 5.09 (m, 1 H), 4.79 (br s, 1 H), 4.34 (m, 1 H), 3.83 (m, 1 H), 2.32 (m, 2 H), 2.01 (m, 1 H), 1.76 (m, 1 H), 1.57 (sext,  $^3J$  = 7.4 Hz, 2 H), 1.23 (d,  $^3J$  = 6.2 Hz, 3 H) and 1.00 (t,  $^3J$  = 7.4 Hz, 3 H). Identified  $^1\text{H}$  NMR signals corresponding to the minor isomer: 6.03 (dt,  $^3J$  = 11.7 Hz,  $^3J$  = 7.4 Hz, 1 H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  162.8 (C), 147.4 (C), 146.3 (C), 138.5 (CH), 129.9 (CH), 127.2 (CH), 124.7 (CH), 124.2 (CH), 123.79 (C), 123.78 (CH), 108.8 (CH), 63.7 (CH), 63.0 ( $\text{CH}_2$ ), 39.9 ( $\text{CH}_2$ ), 35.6 ( $\text{CH}_2$ ), 22.9 ( $\text{CH}_3$ ), 22.3 ( $\text{CH}_2$ ) and 13.9 ( $\text{CH}_3$ ). HRMS (ESI+): Calc'd for  $\text{C}_{18}\text{H}_{24}\text{NO}_2$  [ $\text{M} + \text{H}$ ] $^+$ : 286.1807; found: 286.1806.

2-((3-Methylbut-3-en-1-yl)oxy)-4-(pent-1-en-1-yl)quinoline (**6g**). Prepared from **1a** (50 mg, 0.105 mmol) and 2-methylprop-2-en-1-ol (**5g**) (215  $\mu\text{L}$ , 2.1 mmol, 20 equiv). The reaction was complete after 45 min at 70  $^\circ\text{C}$ . The product was purified via column chromatography ( $\text{SiO}_2$ , *n*-pentane/ $\text{Et}_2\text{O}$  20:1 (*v/v*)) to yield **6g** as an oil (22 mg, 0.078 mmol, yield: 75%, *E/Z* = 97:3).  $R_f$  = 0.65 (*n*-pentane/ $\text{Et}_2\text{O}$  20:1 (*v/v*)).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97 (dd,  $^3J$  = 8.3 Hz,  $^4J$  = 1.0 Hz, 1 H), 7.84 (dd,  $^3J$  = 8.3 Hz,  $^4J$  = 0.8 Hz, 1 H), 7.60 (ddd,  $^3J$  = 8.3 Hz,  $^3J$  = 6.8 Hz,  $^4J$  = 1.4 Hz, 1 H), 7.37 (ddd,  $^3J$  = 8.2 Hz,  $^3J$  = 7.0 Hz,  $^4J$  = 1.3 Hz, 1 H), 6.97 (d,  $^3J$  = 15.8 Hz, 1 H), 6.94 (s, 1 H), 6.42 (dt,  $^3J$  = 15.5 Hz,  $^3J$  = 7.0 Hz, 1 H), 4.85 (s, 2 H), 4.59 (t,  $^3J$  = 6.8 Hz, 2 H), 2.55 (t,  $^3J$  = 6.8 Hz, 2 H), 2.30 (m, 2 H), 1.85 (s, 3 H), 1.56 (sext,  $^3J$  = 7.4 Hz, 2 H) and 1.00 (t,  $^3J$  = 7.4 Hz, 3 H). Identified  $^1\text{H}$  NMR signals corresponding to the minor isomer: 6.01 (dt,  $^3J$  = 11.6 Hz,  $^3J$  = 7.4 Hz, 1 H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  162.4 (C), 147.2 (C), 146.6 (C), 142.7 (C), 137.8 (CH), 129.3 (CH), 127.8 (CH), 124.9 (CH), 123.83 (C), 123.78 (CH), 123.7 (CH), 112.0 ( $\text{CH}_2$ ), 108.9 (CH), 64.1 ( $\text{CH}_2$ ), 37.3 ( $\text{CH}_2$ ), 35.6 ( $\text{CH}_2$ ), 22.9 ( $\text{CH}_3$ ), 22.4 ( $\text{CH}_2$ ) and 13.9 ( $\text{CH}_3$ ). HRMS (ESI+): Calc'd for  $\text{C}_{19}\text{H}_{24}\text{NO}$  [ $\text{M} + \text{H}$ ] $^+$ : 282.1858; found: 282.1863.

(*E*)-2-(Benzo[d][1,3]dioxol-5-ylmethoxy)-4-(pent-1-en-1-yl)quinoline (**6h**). Prepared from **1a** (50 mg, 0.105 mmol) and benzo[d][1,3]dioxol-5-ylmethanol (**5h**) (320 mg, 2.1 mmol, 20 equiv). The reaction was complete after 30 min at 70  $^\circ\text{C}$ . The product was purified via column chromatography ( $\text{SiO}_2$ , *n*-pentane/ $\text{Et}_2\text{O}$  20:1 (*v/v*)) to yield (*E*)-**6h** as an oil (21 mg, 0.06 mmol, yield: 58%).  $R_f$  = 0.48 (*n*-pentane/ $\text{Et}_2\text{O}$  20:1 (*v/v*)).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98 (dd,  $^3J$  = 8.3 Hz,  $^4J$  = 1.1 Hz, 1 H), 7.86 (dd,  $^3J$  = 8.3 Hz,  $^4J$  = 1.0 Hz, 1 H), 7.61 (ddd,  $^3J$  = 8.3 Hz,  $^3J$  = 6.9 Hz,  $^4J$  = 1.4 Hz, 1 H), 7.39 (ddd,  $^3J$  = 8.3 Hz,  $^3J$  = 6.9 Hz,  $^4J$  = 1.3 Hz, 1 H), 7.04 (d,  $^4J$  = 1.6 Hz, 1 H), 7.00 (dd,  $^3J$  = 7.9 Hz,  $^4J$  = 1.6 Hz, 1 H), 6.98 (s, 1 H), 6.97 (d,  $^3J$  = 15.6 Hz, 1 H), 6.82 (d,  $^3J$  = 7.9 Hz, 1 H), 6.40 (dt,  $^3J$  = 15.6 Hz,  $^3J$  = 7.0 Hz, 1 H), 5.96 (s, 2 H), 5.44 (s, 2 H), 2.30 (m, 2 H), 1.56 (sext,  $^3J$  = 7.4 Hz, 2 H) and 0.99 (t,  $^3J$  = 7.4 Hz, 3 H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  162.0 (C), 147.8 (C), 147.4 (C), 147.1 (C), 146.8 (C), 138.0 (CH), 131.3 (C), 129.4 (CH), 127.9 (CH), 124.8 (CH), 124.0 (CH), 123.9 (C), 123.7 (CH), 122.3 (CH), 109.3 (CH), 108.9 (CH), 108.3 (CH), 101.2 ( $\text{CH}_2$ ), 67.6 ( $\text{CH}_2$ ), 35.6 ( $\text{CH}_2$ ), 22.4 ( $\text{CH}_2$ ) and 13.9 ( $\text{CH}_3$ ). HRMS (ESI+): Calc'd for  $\text{C}_{22}\text{H}_{22}\text{NO}_3$  [ $\text{M} + \text{H}$ ] $^+$ : 348.1600; found: 348.1601.

2-(4-Fluorophenyl)ethoxy)-4-(pent-1-en-1-yl)quinoline (**6i**). Prepared from **1a** (50 mg, 0.105 mmol) and 2-(4-fluorophenyl)ethanol (**5i**) (130  $\mu\text{L}$ , 1.05 mmol, 10 equiv). The reaction was complete after 40 min at 70  $^\circ\text{C}$ . The product was purified via column chromatography ( $\text{SiO}_2$ , *n*-pentane/ $\text{Et}_2\text{O}$  98:2 (*v/v*)) to yield **6i** as a white solid (14 mg, 0.04 mmol, yield: 40%, *E/Z* = 98:2). Mp 48–49  $^\circ\text{C}$ .  $R_f$  = 0.53 (*n*-pentane/ $\text{EtOAc}$  95:5 (*v/v*)).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.96 (d,  $^3J$  = 8.2 Hz, 1 H), 7.81 (d,  $^3J$  = 8.4 Hz, 1 H), 7.59 (ddd,  $^3J$  = 8.2 Hz,

$^3J = 7.0$  Hz,  $^4J = 1.3$  Hz, 1 H), 7.37 (ddd,  $^3J = 8.2$  Hz,  $^3J = 7.0$  Hz,  $^4J = 1.1$  Hz, 1 H), 7.29–7.27 (m, 2 H), 7.00 (m, 2 H), 6.96 (d,  $^3J = 15.6$  Hz, 1 H), 6.91 (s, 1 H), 6.40 (dt,  $^3J = 15.6$  Hz,  $^3J = 7.0$  Hz, 1 H), 4.66 (t,  $^3J = 7.0$  Hz, 2 H), 3.11 (t,  $^3J = 7.0$  Hz, 2 H), 2.30 (m, 2 H), 1.56 (sext,  $^3J = 7.4$  Hz, 2 H) and 1.00 (t,  $^3J = 7.4$  Hz, 3 H). Identified  $^1\text{H}$  NMR signals corresponding to the minor isomer: 6.02 (dt,  $^3J = 11.7$  Hz,  $^3J = 7.4$  Hz, 1 H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  161.7 (d,  $^1J_{\text{C-F}} = 242$  Hz, C), 162.2 (C), 147.2 (C), 146.7 (C), 137.9 (CH), 134.5 (d,  $^4J_{\text{C-F}} = 3$  Hz, C), 130.6 (d,  $^3J_{\text{C-F}} = 8$  Hz, CH), 129.4 (CH), 127.8 (CH), 124.8 (CH), 123.9 (CH), 123.8 (C), 123.7 (CH), 115.3 (d,  $^2J_{\text{C-F}} = 21$  Hz, CH), 108.8 (CH), 66.3 ( $\text{CH}_2$ ), 35.6 ( $\text{CH}_2$ ), 34.8 ( $\text{CH}_2$ ), 22.4 ( $\text{CH}_2$ ) and 13.9 ( $\text{CH}_3$ ).  $^{19}\text{F}\{\text{H}\}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.0. HRMS (ESI+): Calc'd for  $\text{C}_{22}\text{H}_{23}\text{NOF}$   $[\text{M} + \text{H}]^+$ : 336.1764; found: 336.1761.

(*E*)-2-Ethoxy-4-(buta-1,3-dien-1-yl)quinoline (**7a**). Prepared from *N*-(7-(benzyloxy)hepta-1,3-dien-1-yl)-*N*-(2-iodophenyl)-4-methylbenzenesulfonamide (**1b**) (57 mg, 0.1 mmol) and EtOH (**5b**) (120  $\mu\text{L}$ , 2.0 mmol, 20 equiv). The reaction was complete after 50 min at 70 °C. The product was purified via column chromatography ( $\text{SiO}_2$ , *n*-pentane/EtOAc 98:2 (*v/v*)) to yield (*E*)-**7a** as a white solid (7 mg, 0.03 mmol, yield: 30%). Mp 64–65 °C.  $R_f = 0.4$  (*n*-pentane/EtOAc 98:2 (*v/v*)).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97 (dd,  $^3J = 8.3$  Hz,  $^4J = 1.1$  Hz, 1 H), 7.83 (dd,  $^3J = 8.3$  Hz,  $^4J = 0.7$  Hz, 1 H), 7.61 (ddd,  $^3J = 8.3$  Hz,  $^3J = 6.9$  Hz,  $^4J = 1.4$  Hz, 1 H), 7.38 (ddd,  $^3J = 8.3$  Hz,  $^3J = 6.9$  Hz,  $^4J = 1.3$  Hz, 1 H), 7.17 (br d,  $^3J = 15.4$  Hz, 1 H), 7.01 (s, 1 H), 6.95 (ddt,  $^3J = 15.4$  Hz,  $^3J = 10.5$  Hz,  $^4J = 0.7$  Hz, 1 H), 6.64 (dddd,  $^3J = 16.9$  Hz,  $^3J = 10.6$  Hz,  $^3J = 10.0$  Hz,  $^4J = 0.7$  Hz, 1 H), 5.47 (dddd,  $^3J = 16.9$  Hz,  $^2J = 1.4$  Hz,  $^4J = 0.7$  Hz,  $^5J = 0.7$  Hz, 1 H), 5.34 (dddd,  $^3J = 10.0$  Hz,  $^2J = 1.4$  Hz,  $^4J = 0.7$  Hz,  $^5J = 0.7$  Hz, 1 H), 4.53 (q,  $^3J = 7.1$  Hz, 2 H) and 1.45 (t,  $^3J = 7.1$  Hz, 3 H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  162.3 (C), 147.4 (C), 145.3 (C), 136.8 (CH), 135.5 (CH), 129.5 (CH), 128.0 (CH), 127.0 (CH), 123.9 (CH), 123.6 (C), 123.4 (CH), 120.6 ( $\text{CH}_2$ ), 108.7 (CH), 61.7 ( $\text{CH}_2$ ) and 14.8 ( $\text{CH}_3$ ). HRMS (ESI+): Calc'd for  $\text{C}_{15}\text{H}_{16}\text{NO}$   $[\text{M} + \text{H}]^+$ : 226.1232; found: 226.1233.

(*E*)-5-(2-((4-(buta-1,3-dien-1-yl)quinolin-2-yl)oxy)ethyl)-4-methylthiazole (**7b**). Prepared from **1b** (50 mg, 0.088 mmol) and 2-(4-methylthiazol-5-yl)ethanol (**5c**) (210  $\mu\text{L}$ , 1.8 mmol, 20 equiv). The reaction was complete after 50 min at 70 °C. The product was purified via column chromatography ( $\text{SiO}_2$ , *n*-pentane/EtOAc/ $\text{Et}_3\text{N}$  90:10:1 (*v/v/v*)) to yield (*E*)-**7b** (6 mg, 0.019 mmol, yield: 21%) as an oil.  $R_f = 0.19$  (*n*-pentane/EtOAc 90:10 (*v/v*)).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.60 (s, 1 H), 7.99 (dd,  $^3J = 8.3$  Hz,  $^4J = 0.9$  Hz, 1 H), 7.83 (dd,  $^3J = 8.3$  Hz,  $^4J = 0.7$  Hz, 1 H), 7.62 (ddd,  $^3J = 8.3$  Hz,  $^3J = 6.9$  Hz,  $^4J = 1.3$  Hz, 1 H), 7.41 (ddd,  $^3J = 8.2$  Hz,  $^3J = 7.0$  Hz,  $^4J = 1.2$  Hz, 1 H), 7.18 (d,  $^3J = 15.5$  Hz, 1 H), 7.02 (s, 1 H), 6.96 (dd,  $^3J = 15.4$  Hz,  $^3J = 10.6$  Hz, 1 H), 6.65 (ddd,  $^3J = 16.9$  Hz,  $^3J = 10.4$  Hz,  $^3J = 10.1$  Hz, 1 H), 5.50 (d,  $^3J = 16.9$  Hz, 1 H), 5.36 (d,  $^3J = 10.0$  Hz, 1 H), 4.65 (t,  $^3J = 6.7$  Hz, 2 H), 3.31 (t,  $^3J = 6.7$  Hz, 2 H) and 2.49 (s, 3 H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  161.8 (C), 149.94 (C), 149.88 (CH), 147.2 (C), 145.6 (C), 136.8 (CH), 135.7 (CH), 129.7 (CH), 128.0 (CH), 127.7 (C), 126.8 (CH), 124.2 (CH), 123.7 (C), 123.5 (CH), 120.8 ( $\text{CH}_2$ ), 108.4 (CH), 65.5 ( $\text{CH}_2$ ), 26.3 ( $\text{CH}_2$ ) and 15.2 ( $\text{CH}_3$ ). HRMS (ESI+): Calc'd for  $\text{C}_{19}\text{H}_{19}\text{N}_2\text{OS}$   $[\text{M} + \text{H}]^+$ : 323.1218; found: 323.1218.

### 3.3. Deuterium Labeling Experiments

1,3-butadiynamide **1a** (48 mg, 0.10 mmol), tetrakis(triphenylphosphine)palladium(0) (12 mg, 0.01 mmol, 10 mol%) and *t*-BuOK (28 mg, 0.25 mmol, 2.5 equiv) were introduced in a dry Schlenk tube under argon atmosphere. Then  $\text{CD}_3\text{OD}$  (0.75 mL) was added. The Schlenk tube was sealed and immediately placed in an oil bath preheated to 70 °C. After 30 min, the reaction mixture was diluted with EtOAc and washed with brine. After drying ( $\text{MgSO}_4$ ), the organic layer was filtered and evaporated under reduced pressure. The product was purified via column chromatography ( $\text{SiO}_2$  pretreated with *n*-pentane/ $\text{Et}_2\text{O}$ / $\text{Et}_3\text{N}$  94:2:2 (*v/v/v*), *n*-pentane/ $\text{Et}_2\text{O}$  98:2 to 95:5 (*v/v*)) to yield **8a** as an oil (13.5 mg, 0.058 mmol, yield: 58%).  $R_f = 0.72$  (*n*-pentane/ $\text{Et}_2\text{O}$  10:1 (*v/v*)).

*D*<sub>5</sub>-2-Methoxy-4-(pent-1-en-1-yl)quinoline (**8a**).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98 (dd,  $^3J = 8.3$  Hz,  $^4J = 1.0$  Hz, 1 H, H<sub>5</sub>), 7.90 (m, 1 H, H<sub>8</sub>), 7.62 (ddd,  $^3J = 8.3$  Hz,  $^3J = 7.0$  Hz,  $^4J = 1.2$  Hz, 1 H, H<sub>7</sub>), 7.39 (ddd,  $^3J = 8.1$  Hz,  $^3J = 7.0$  Hz,  $^4J = 1.0$  Hz, 1 H, H<sub>6</sub>), 6.42 (tt,  $^3J = 7.0$  Hz,  $^3J = 2$  Hz, 1 H, H<sub>12</sub>), 2.32 (q<sub>app</sub>,  $^3J = 7.2$  Hz, 2 H, H<sub>13</sub>), 1.57 (sext,  $^3J = 7.4$  Hz, 2 H,

H<sub>14</sub>) and 1.00 (t, <sup>3</sup>J = 7.4 Hz, 3 H, H<sub>15</sub>). HRMS (ESI+): Calc'd for C<sub>15</sub>H<sub>13</sub>D<sub>5</sub>NO [M + H]<sup>+</sup>: 233.1702; found: 233.1704.

#### 4. Conclusions

In conclusion, we have developed a straightforward Pd-catalyzed route to 2-alkoxy 4-alkenylquinolines starting from readily accessible 1,3-butadiynamides. Classic synthetic methods for 2-alkoxyquinolines rely on modifications of the quinoline core and usually yield quinolines with simple alkoxy moieties at the 2-position. By contrast, the presented synthesis strategy is based on the de novo assembly of the 2-alkoxyquinoline core from acyclic precursors—1,3-butadiynamides and primary alcohols as external nucleophiles—to access a highly varied set of 2-alkoxyquinoline derivatives that are otherwise difficult to obtain. The removal of the ynamide tosyl group occurs under defined reaction conditions, which include the use of TBAF/KOH in THF. This initiates the in situ generation of highly reactive and sensitive ketenimine and/or [4]cumulenimine species, which trigger a palladium-catalyzed cascade reaction involving bond formation and cleavage as well as several tautomeric isomerization steps, ultimately leading to highly functionalized 2-alkoxyquinolines.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules29153505/s1>, Experimental procedures and characterization data of 1,3-butadiynamides **1a,b** [32,33] and NMR spectra for all new compounds.

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